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Clinical forms and diagnosis of tuberculosis

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ABSTRACT

Tuberculosis is an infectious disease whose diagnosis dates back to very early ages, which still maintains its importance in the world and in our country, can be treated and prevented with preventive (prophylactic) treatment. It is one of the leading causes of death in HIV/AIDS positive patients. Tuberculosis can be seen in two ways, mainly lung tuberculosis and extra-pulmonary tuberculosis. Tuberculosis forms other than lung and laryngeal tuberculosis are not contagious. Today, the HIV epidemic and international migration are the main causes of the increase in the number of tuberculosis cases. In this collected work, lung and non-pulmonary forms of tuberculosis, clinical diagnosis, and current developments in diagnosis are summarized.

Keywords: Tuberculosis, pulmonary tuberculosis, extra-pulmonary tuberculosis, diagnosis, new diagnostic tests

INTRODUCTION

Tuberculosis is still one of the leading causes of death among treatable infectious diseases. It continues to be an important public health problem all over the world and in Turkey.[1] Before the COVID-19 pandemic, it was the most important public health problem and was among the infectious diseases that most frequently caused death.

EPIDEMIOLOGY OF TUBERCULOSIS

Tuberculosis ranks 9th-13th among the causes of death due to infectious diseases all over the world. According to the World Health Organization's 2020 report, there is approximately 10 million tuberculosis (TB) patients worldwide. The increase in the number of immunosuppressive patients, especially HIV epidemic and HIV, is the most important risk factor for the increase in the number of tuberculosis cases. In addition, international migrations also pose a risk in terms of the spread of the disease. Most patients with tuberculosis live in Asia's most populous countries, Bangladesh, China, India, Indonesia and Pakistan, which account for half (48%) of new cases each year.[2]

In Turkey, 11,401 TB patients were reported in 2019.[3]

MYCOBACTERIA CAUSING TUBERCULOSIS

The causative agent of tuberculosis is the human pathogen *Mycobacterium tuberculosis* (*M. tuberculosis*).

Less frequently, located in the *M. tuberculosis* complex; *M. bovis* (zoonosis), *M. africanum* (human pathogen), *M. microti* (zoonosis, can be transmitted from rodent to human), *M. caprae* (human and animal pathogen), and *M. pinnipedii* (from seals to humans) may also be causative.[4] Tuberculosis can hold almost all organs and tissues, except hair and nails.

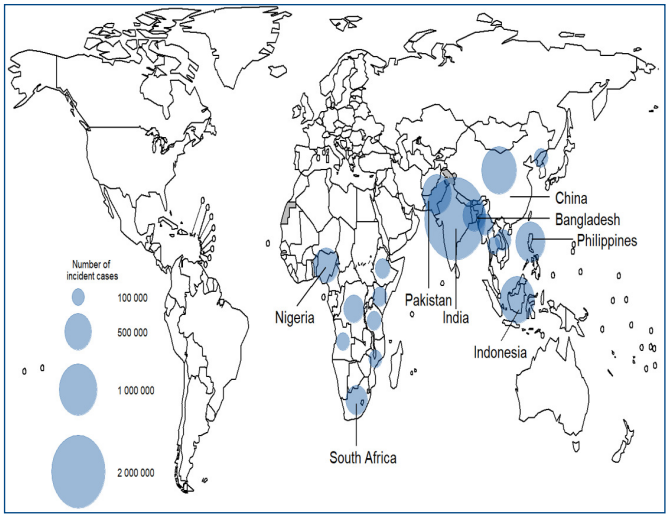

Figure 1*. Eight countries (Nigeria, South Africa, Pakistan, India, Indonesia, China, Bangladesh and the Philippines), which are in the top eighth place in terms of number of cases and account for two-thirds of global cases in 2020

(*) Retrieved from source 2

CLINICAL FORMS OF TUBERCULOSIS

Tuberculosis can be seen in two clinical forms, mainly pulmonary TB and extra-pulmonary TB (EPTB). EPTB can be grouped mainly as TB lymphadenitis (Scrofula), miliary TB, TB meningitis, TB pleurisy, TB pericarditis, TB spondylodiscitis (Pott's disease), and other forms.

LUNG TB AND DIAGNOSIS

Patient's anamnesis, physical examination findings, pulmonary film and pulmonary TB are suspected. The

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definitive diagnosis of lung TB is bacteriological. At least three sputum samples should be taken from patients with suspected lung, pleura, larynx, and miliary TB. The most ideal for sputum samples is the examination of the first sputum in the morning for three days. Induced sputum or fasting gastric juice is examined 3 times in patients who cannot expectorate. If the sample cannot be taken, bronchoscopic lavage fluid is taken. The ideal is to examine the first sputum in the morning for 3 days.

The amount of sputum should be 3-5 ml, a post-condensation examination should be performed. Diagnosis rate increases with condensation (decontamination/concentration). Sensitivity is low in non-cavitary disease and HIV-positive patients.

NaOH-NALC (N-acetyl-L-cysteine (Cubica method) is the most commonly used method for condensation.5 Sensitivity increases by 10% in the second sputum sample and by 2% in the third sample.[4] After microscopic examination of the sputum, the remaining sputum samples should be added to both broth and agar mediums. In broth mediums (mgit, Bactec 460, TK medium, etc.), the reproduction rate and reproduction ratio are generally higher. It is recommended that each patient undergo a culture and drug susceptibility test (DST) at the beginning of treatment. Xpert MTB/Rif test, which is one of the molecular tests, should be applied to determine both rapid diagnosis and RİF resistance.[5]

EXTRAPULMONARY TUBERCULOSIS (EPTB)

Tuberculosis bacilllus can hold all organs and systems. EPTB is responsible for approximately 15-25% of all tuberculosis cases. EPTB may occur with or without lung involvement. It is especially common in HIV-positive patients.

EPTB Pathogenesis

EPTB can develop in three main ways:

1. Spread from superficial mucosal foci: Spread of infectious pulmonary secretions from the respiratory and gastrointestinal system superficial mucosa
2. Neighborhood (direct) spread: Spread from a subpleural focus to the pleural cavity
3. It may develop as a result of lymphohematogenic spread from established chronic lung or extra-pulmonary foci during primary infection.[4]

EPTB in Turkey

According to the 2019 data of the Department of Tuberculosis War, the number of EPTB cases in women in Turkey is 2393 (47.8%) and 1655 (24.4%) in men, and the number of EPTB cases in women is higher. According to the same report, the number of lung TB cases was 4766 (70.3%) in males and 2351 (46.9%) in females, and the number of lung TB cases was higher in males than in females.[3]

EPTB Diagnosis

Detailed anamnesis and physical examination should be performed. In the diagnosis of EPTB, microscopic examination (EZN, Auramine-Rhodamine staining), culture, molecular diagnostic methods (polymerase chain reaction, etc.) and serological tests can be used. Histopathological examination should also be performed.

Clinical Forms of EPTB

Tuberculous lymphadenitis (Scrofula): Lymphadenitis is the most common form of EPTB. The tuberculin skin test (purified protein derivative; PPD) is mostly positive. It most commonly occurs as a painless, firm mass along the upper border of the sternocleidomastoid muscle.

Lymphadenopathy outside the cervical and supraclavicular area usually indicates more severe TB with systemic symptoms. Fine-needle aspiration cytology shows granuloma, but smear microscopy or cultures are usually negative. Histopathological imaging may also be seen in other mycobacterial or fungal infections.

The culture of the biopsy material is necessary for diagnosis. The culture of biopsy material is required for diagnosis.[4]

In the diagnosis, the sensitivity and specificity of the Xpert Ultra test in lymph node aspirate, one of the molecular tests, were reported to be 70% and 100%, respectively.[6]

Mediastinal TB Lymphadenitis: During primary infection, mediastinal adenopathy can be seen frequently radiographically, especially in children. Mediastinal lymphadenopathy is common in patients with HIV/AIDS positive TB.

The presence of low-density areas in the lymph nodes on CT scan suggests TB, however; mediastinoscopy is usually required for diagnosis. Diagnosis is made by microscopic examination (EZN staining) and culture of biopsy material taken by mediastinoscopy.

Fibrosing Mediastinitis: TB can cause fibrosing mediastinitis. Patients may present with shortness of breath with exertion due to compression of the pulmonary veins and arteries or, less frequently, with superior vena cava syndrome. Hilar lymphadenopathy or active lung disease is rarely found. Thoracotomy is required for diagnosis.

Mesenteric TB lymphadenitis: Involvement is often intra-abdominal, and sometimes obstruction may develop in the bile ducts, ureters, or intestine. Low-density centers and peripheral contrast enhancement are observed in the lymph nodes. Involvement is more often intraabdominal than retroperitoneal, and sometimes obstruction is observed in the bile ducts, ureters, or intestine. Diagnosis is made by microscopic examination and culture of biopsy material.[4]

2. Miliary TB

It defines progressive disseminated hematogenous TB. It accounts for approximately 1% of all TB cases.[4] Miliary TB is defined as the detection of miliary organ involvement in at least two separate organs that are not adjacent to each other in biopsy or autopsy. The presence of tubercle is the main condition for diagnosis.[7] Pleural effusion, peritonitis or meningitis are observed in 3/2 of the affected cases. Physical examination is generally not specific, but may provide a careful examination and biopsy diagnosis for cutaneous eruptions, sinus tracts, scrotal masses, and lymphadenopathy.[4] Choroidal tubercle is an important finding in the eye examination in 15-21% of cases.[7]

Miliary infiltrate is the most useful finding on chest radiography and is the possible cause of suspected miliary TB (**Figure 2**)

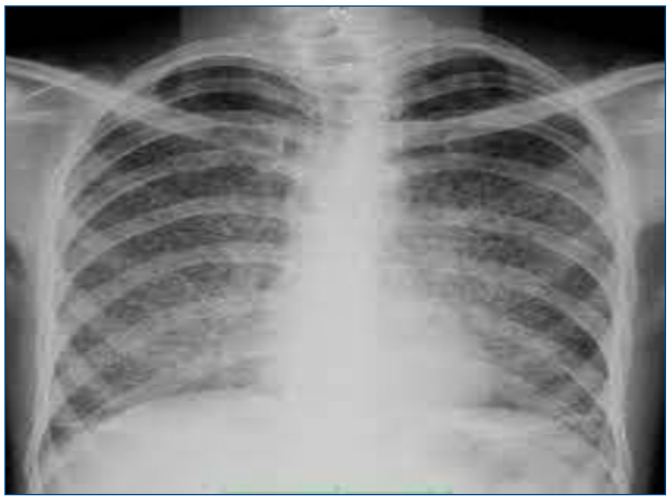

Figure 2. Micronodules on high-resolution lung CT (nodular infiltrative view showing patchy glass view in places on the right)

Micronodules can be detected in high-resolution lung CT, its sensitivity is superior to PA chest X-ray (**Figure 3**).

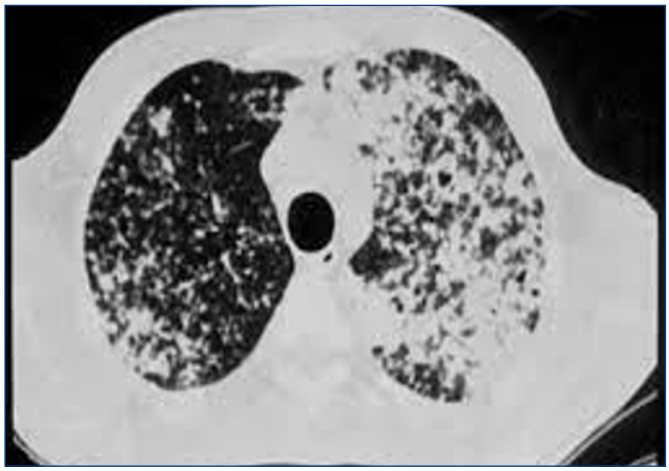

Figure 3. Micronodules on high-resolution lung CT (nodular infiltrative view showing patchy glass view in places on the right)

Diagnosis is usually made by examination of tissue (lymph nodes, scrotal masses, if any, liver biopsy or bone marrow samples). Blood cultures for mycobacteria may also be positive. Tissue sampling by transbronchial biopsy is valuable for diagnosis. The detection of cashed granuloma or acid-resistant bacilli is diagnostic. The sensitivity of molecular tests (e.g. PCR) to detect *M. tuberculosis* body fluid and tissue samples in the diagnosis of miliary TB has been reported to be between 37-100%.[6]

3. Primary Hepatic TB

Rarely, miliary TB may mimic cholangitis with fever, liver function test abnormalities suggestive of obstructive disease, and little evidence of hepatocellular disease. The diagnosis of primary hepatic TB is made by liver biopsy.[4]

4. TB Meningitis

The clinic begins with resentment, intermittent headaches, and a low level of fever. Then, within 2-3 weeks, long-term headache, vomiting, confusion, meningismus and focal neurological symptoms develop.[4] If left untreated, the mortality rate and sequellae development rate are high.[8] TB meningitis and miliary TB are the most severe forms of tuberculosis. Cases of TB meningitis, if left untreated, result in death within 5-8 weeks.[8]

The clinical spectrum can range from chronic headache or mild mental status changes to sudden, severe meningitis that progresses to coma. Fever may not be seen, and the number of leukocytes is usually normal. Hyponatremia due to mild anemia and inappropriate ADH secretion is common. Concomitant extrameningeal TB evidence is available in ¾ of the cases. In most cases, there are no clinical or anamnesis clues to suggest TB.[4]

Tuberculous meningitis is seen in 3 stages:

- **Stage-1;** Conscious, no focal neurological symptoms and hydrocephalus.
- **Stage-2;** Confusion and focal neurological findings; cranial nerve paralysis, hemiparesis
- **Stage-3;** Stupor or pronounced paraplegia, hemiplegia.[9,10]

The basis of diagnosis is the examination of CSF. The number of cells usually ranges from 0 to 1500/mm³, the amount of protein is increased, CSF glucose is characteristically low. Lymphocytic cell is dominant in CSF. Identification of bacilli often requires examination of large volumes of CSF taken by recurrent lumbar puncture. PPD skin test has a sensitivity of 62% and a specificity of 82%.[4]

The Interferon Gamma Release Assay (IGRA) sensitivity has been reported as 72% in CSF, 69% in blood, and its specificity in CSF is 97%, 89% in blood. It has been reported that PCR test in CSF is positive in roughly 60% to 90% of culture-positive CSF samples.[11]

In a meta-analysis, when the Xpert Ultra test was compared with the culture, it was reported to have 89.4% sensitivity and 91.2 specificity.[6] In another study, the sensitivity and specificity of lipoarabinomannan (LAM) test in CSF in the diagnosis of TB meningitis were reported to be 52% and 98%, respectively.[12]

5. TB Pleurisy (Effusion Serofibrinous pleurisy)

Pleural fluid typically contains 500-2500 leukocytes/mm³ and contains more than 90% lymphocytes. The level of pleural fluid protein is usually more than 2.5 g/dL, the glucose concentration is generally moderately low compared to serum values, rarely below 20 mg/dL. Increased pleural fluid adenosine deaminase levels are highly sensitive and specific for tuberculous pleurisy, however; much lower limit values should be used in patients over 45 years. Open pleural biopsy or thoracoscopy is required in almost all cases for diagnosis.[4]

When the Xpert Ultra test, one of the molecular tests in the diagnosis, was compared with the pleural fluid culture, its sensitivity was determined as 75% and its specificity as 87%.[6]

6. TB Pericarditis

Tuberculous pericarditis most commonly develops as a result of spread from mediastinal or hilar lymph nodes. Echocardiography shows effusion and a large number of loculations suggestive of TB can be detected. Pericardiocentesis is indicated to provide hemodynamics. In some cases, biopsy shows only nonspecific inflammation. Tuberculous pericardial fluid shows many features of TB pleural fluid; ARB is rarely positive and culture is positive in 50% of cases.[4]

7. Vertebral Tuberculosis (Pott's disease, TB spondylodiscitis)

It often develops as a result of hematogenous spread. TB, which holds the skeletal system, develops as a result of

lymphatic spread from hematogenous focus or pleural disease in 1/3 of cases. The earliest focus is the anterior upper or lower angle of the vertebral body.

This usually spreads to the intervertebral disc and adjacent vertebrae. The classical radiological image is destruction in the intervertebral disc and adjacent vertebral corpus. On physical examination; gibbus palpated from the back can be detected.

The lower thoracic vertebra is most commonly involved, followed by the lumbar vertebra. In endemic countries, Pott's disease is usually seen in older children and young adults, while in developed countries it is seen in older individuals. TB bacilli are infrequent and only 50% of cases are positive for PU or ARB and culture in the tissue.

In histological examination, caseification with or without caseification can be detected in ¾ of the cases. Abscess and sinus formation develops in 50% or more of paraspinal cold abscesses, in some cases after treatment has begun. In some cases, the lesion can only be seen by CT or MRI.

The abscess can sometimes spread the infection to distant vertebral corpuses without affecting the intervening vertebrae.

Epidural or psoas abscess can also complicate TB spondylitis. The interferon gamma release assey (IGRA) tests and PPD skin test can be used to support the diagnosis. In one study, the sensitivity rate of IGRA test in Pott's disease was reported as 84% and the specificity rate as 95%.[13]

8. Peripheral Osteoarticular TB

Peripheral tuberculous arthritis is in the form of chronic, slowly progressive monoarthritis in 90% of the cases. It most commonly involves the hips or knees. A history of trauma is common, followed by slow progression of inflammation weeks or months later. Systemic symptoms in the elderly population are seen as multiple joint involvement and periarticular abscess formation. It can cause hand tenosynovitis, wrist arthritis, and carpal tunnel syndrome. The earliest symptom of tuberculous arthritis is pain that appears weeks or months before signs of inflammation and radiographic changes.

Initially, soft tissue swelling, later osteopenia, periarticular bone destruction, periosteal thickening, and eventually cartilage and bone destruction can be seen on the radiograph. Cold abscesses and drainage sinuses are often seen in chronic cases. Biopsy is required for diagnosis. TB osteomyelitis can involve any bone, including the ribs, skull, phalanx, pelvis, and long bones. TB is the most common infectious cause of single or multiple osteomyelitic rib lesions.[4]

9. Renal TB

It develops after hematogenous spread. Asymptomatic renal cortical foci can be detected in all forms of TB. The time between infection and active kidney disease is usually years, and sometimes a decade (10 years). Local symptoms are predominant and advanced tissue destruction may occur long before the diagnosis. Contrast-enhanced abdominal CT is usually abnormal. Fever, weakness, dysuria, pollacuria, side pain, hematuria (50% of cases) may occur. Hydronephrosis, parenchymal cavitation and autonephrectomy may be seen in the advanced stage. Focal calcification is particularly suggestive of the disease. The disease is usually one-sided. Sterile pyuria, hematuria and proteinuria are common in renal TB. Three urine cultures taken 3 times in the morning make the diagnosis in 80%-90% of cases. If there is a renal abnormality, however; If the urine cultures are negative, the culture of the material obtained by cytological examinations and fine-needle biopsy may be diagnostic. PPD skin test is positive between 88-95% in patients with renal TB.[4]

10. Male genital TB

80% of male genital TB is associated with concomitant renal disease. In advanced stage renal TB, involvement in genital organs accompanies. The infection spreads from the renal focus to the prostate, seminal vesicles, epididymis and testicles, respectively. The most common clinical finding is a sensitive or drained sinus containing scrotal mass. It may cause oligospermia and infertility. Epididymal or prostate calcification suggests a diagnosis; however, prostate calcification is also seen in chronic prostatitis. The definitive diagnosis is usually made by biopsy.[4]

11. Female Genital TB

It starts from the focus in the first endosalpinx by hematogenous route, from there it can spread to the endometrium, ovaries, cervix, and vagina. It may resemble a mass carcinoma to a granulomatous ulcer in the cervix. Common complaints are infertility or menstrual irregularities and abdominal pain. The clinical picture suggests pelvic inflammatory disease that does not respond to treatment. Spread to the peritoneum may be seen. Pelvic TB can cause ectopic pregnancy. Tubovarian abscess can be detected on CT, multiloculated mass can be detected in the ovary. Menstrual blood or endometrial scraping cultures may be positive, but the diagnosis is often made by examining the tissue taken during surgery. The response to antituberculosis treatment is quite good. Surgical intervention may be required only for residual large tuboovarian abscesses.

12. Gastrointestinal TB

Gastrointestinal tuberculosis can involve any region from the mouth to the perianal region.[4,14] The most common involvement is in the ileocecal region. The disease can be seen as a result of swallowing the infected sputum of patients with advanced cavitary lung or laryngeal TB or drinking the milk of an animal infected with Mycobacterium bovis.

Radiological evidence of lung TB is less common. Ulcers that do not heal in the tongue or oropharynx and ulcers that do not heal after tooth extraction may be due to TB.

Obstruction or tracheoesophageal fistula formation may be seen in esophageal involvement. Stomach and duodenal involvement may cause ulcerative lesion, obstruction, or peptic ulcer findings. Small bowel involvement may cause perforation, obstruction, enteroenteric and enterocutaneous fistulas, massive bleeding, and severe malabsorption. In ileocecal region involvement, abdominal pain, anorexia, diarrhea, obstruction, sometimes severe bleeding and often palpable mass can be detected.[4]

Clinical forms of gastrointestinal TB:

- **Pancreatic TB:** It may occur as an abscess or a mass that holds regional nodes and resembles a carcinoma.
- **Bile ducts TB:** The bile ducts may be obstructed by tuberculous granuloma and cause tuberculous ascending cholangitis.
- **Granulomatous hepatitis:** Usually asymptomatic. In this case, an elevated alkaline phosphatase that is disproportionately increased with normal transaminase and bilirubin levels can be seen (called primary TB of the liver).

Gastrointestinal TB mostly affects immunocompromised hosts, less frequently it can occur in immunocompromised individuals. Diagnosis is quite difficult as it can mimic malignancy or inflammatory bowel disease. The high clinical suspicion index and the use of many diagnostic methods together allow early diagnosis. Mortality and morbidity rates may decrease with early diagnosis and treatment. Antituberculosis treatment is the same as lung disease and invasive and special surgical interventions may be required in case of development of some complications.[14]

Tanoğlu et al.[15] evaluated 104 patients with gastrointestinal tuberculosis in a multicenter study and 65 (86.6%) of 75 patients who underwent intestinal biopsy were isolated from culture with TB bacilli. Positivity was detected in 35 (94.6%) of 37 biopsy samples by polymerase chain reaction test. *M. tuberculosis* was isolated from acid culture in 11 (57.9%) of 19 patients who received acid samples. Upper gastrointestinal endoscopy was performed in 40 (38.5%) of the patients and colonoscopy was performed in 74 (71.1%) of the patients. Surgical interventions frequently formed the source of diagnostic samples (25 laparoscopy/20 laparotomy, 45 (43.3%) samples in total); 4 (3.8%) of the patients who started antituberculosis drug treatment died, and 2 (1.9%) cases had recurrence.

In the study, the incidence of underlying immunosuppression was found to be high in gastrointestinal TB patients. Most of the patients were diagnosed with surgery, and it was reported that the mortality rate was low with appropriate and rapid diagnosis and treatment.

The definitive diagnosis of gastrointestinal TB can usually be made by surgical intervention or endoscopy, microbiological and histopathological examination of the material taken by colonoscopy.

13. TB Peritonitis

Tuberculous peritonitis is rare in developed countries, but can occur in high-risk patient groups, including patients with AIDS or cirrhosis, patients on continuous outpatient peritoneal dialysis, migrants from regions with high TB endemicity, and immunosuppressed patients. The diagnosis of TB peritonitis requires a high index of clinical suspicion and should be considered in the presence of lymphocyte dominance in peritoneal fluid and acid fluid with a serum-acid albumin gradient <1.1 mg/dl.[16]

Peritoneal fluid is exudative and often the number of cells is between 500-2000. Lymphocytes are typically dominant. ARB is rarely positive in acid fluid, and culture positivity is detected in 25% of cases.[4] The level of adenosine deaminase and interferon-gamma in the acid fluid increases. PPD skin test can be positive in 30% -100% of cases.

Microbiological or pathological confirmation is still the gold standard for diagnosis. The detection rate of the agent in acid fluid cultures is low, but the culture of samples taken by biopsy or peritoneoscopy often confirms the diagnosis.

Ultrasound and computed tomography can be used to guide acid fluid aspiration and peritoneal biopsies. Apart from resistant tuberculosis cases, 6 months of antituberculosis treatment is sufficient.[14]

The definitive diagnosis is often made by peritoneal biopsy.[4]

14. Cutaneous TB

Tuberculosis of the skin develops due to *Mycobacterium tuberculosis* (*M. tuberculosis*), *M. bovis*, and in some cases Bacillus Calmette-Guerin (BCG) (*M. bovis*ine attenuated strain) vaccine. Bacilli come to the skin through exogenous, endogenous or autoinoculation. Endogenous spread can be in three forms: spread to the environment, lymphatic spread, and hematogenous spread. The cellular immune system plays an important role in tuberculosis infection.[17]

Cutaneous TB can be seen in different ways depending on the virulence of the bacterium, its number, the general condition of the host and the immune system. The incidence of cutaneous TB is in line with the incidence of pulmonary tuberculosis in that country. The most common skin forms of TB in Turkey are scrofuloderma (tuberculosis cutis collikuative) and lupus vulgaris forms, other forms are rarely seen. Skin TB may occur as primary infection or reinfection TB.[18]

Skin TB can be classified as primary and secondary skin TB. Primary skin TB can be seen in two forms: tuberculosis primary complex and miliary skin TB. The main forms of secondary skin TB are lupus vulgaris, tuberculosis cutis verrucosa, tuberculosis cutis orificealis and metastatic TB abscesses.

Primary skin TB

1. **TB primary complex (TB chancre):** It is transmitted by the exogenous introduction of bacilli into the skin of people who have not had contact with TB bacilli before. It is often seen on the face and extremities in children.
2. **Miliary skin TB (TB cutis milliaris):** It is an extremely rare form of skin TB. It occurs as a result of the hematogenous spread of Mycobacteria, especially in infants and children, after infections in which the immune system is suppressed, such as measles and scarlet fever.

Secondary skin TB

1. **Lupus vulgaris:** It is the most common form of skin TB. It shows a chronic course and can last for years. It is more common in female gender than men. It often develops as a result of the transmission of TB bacillus from the TB focus in the body to the skin through the hematogenous, lymphogenic, or environmental spread, rarely following the BCG vaccine.
2. **Tuberculosis cutis verrukosa:** It is a verricular skin tuberculosis that occurs due to exogenous reinfection in individuals who have previously been in contact with TB bacilli and are highly immune to bacilli. A high hypersensitivity is detected with the PPD skin test.[17] Skin involvement may result from exogenous vaccination. TB verrucosa cutis is associated with vaccination.[4]
3. **Scrofuloderma (TB cutis colicuativa):** It often develops as a result of the direct spread of lymph node, bone, joint, tendon tuberculosis to the skin. Elementary lesion is gamma.
4. **Tuberculosis cutis orificialis:** It occurs by direct inoculation from the primary focus or by inoculation of mycobacteria into the mucous membranes or skin of the orifices with lymphatic spread in individuals with advanced stage organ TB and compromised immunity.
5. **Metastatic TB abscesses:** It is the form that develops as a result of the hematogenous spread of tuberculosis bacilli from the primary focus, especially in immunodeficiency conditions such as AIDS and in a period when immunity decreases in patients with severe immunodeficiency.[17]

The diagnosis of skin TB is made by microscopic examination, culture, histopathological examination of the skin biopsy material. PPD skin test is also used in diagnosis.

15. TB Laryngitis and Otitis

TB laryngitidis: More than 50% of laryngeal TB cases are caused by hematogenous spread.

TB otitis: Clinically, it is painless ear discharge with multiple tympanic perforations, exuded granulation tissue, early severe hearing loss, and mastoid bone necrosis.

16. Other Clinical Forms

- **Vascular TB:** With or without aneurysm formation, aortic TB may develop as a result of spread from neighboring infected nodes, pericarditis, spondylitis, paravertebral abscesses or empyema. Wide hematogenous spread or aortic rupture may occur.
- **Ocular TB:** Various ocular involvement can be seen, including choroidal tubercles, uveitis, iritis and episcleritis. During miliary TB in areas with high prevalence of TB, choroidal TB (usually asymptomatic) may occur in 5% to 20% of patients.
- **Tbc in the breast:** It can be seen in the form of abscess, sclerosing lesions resembling carcinoma and lesions forming multiple nodules. Diagnosis is made by microscopic examination and culture of biopsy material.4
- **Nasal TB:** It can be seen in the form of destructive nasal lesions similar to Wegener's granulomatosis both clinically and histologically.

TB of the adrenal glands may cause calcified or non-calcified adrenal enlargement such as histoplasmosis. Granulomatous adrenal TB can cause Addison's disease without calcification or adrenal enlargement.[4] Hatipoğlu et al.[19] reported a 60-year-old female patient with renal tuberculosis with Addison's disease.

NEW DIAGNOSTIC TESTS

- Investigation of Lipoarabinomannan (LAM) in Urine or CSF
- Detection of urinary antigen (LAM) is a lateral flow or ELISA test that can be applied to point-of-care testing. It has high susceptibility in untreated advanced AIDS patients (CD4<50 cells/mm³). It has low sensitivity in conditions other than advanced AIDS disease. Recently, tests to detect LAM antigen in CSF have also been used in the diagnosis of TB meningitis.[20]
- Clustered regularly interspaced short palindromic repeat (CRISPR; regular interval palindromic repeat Clusters) –*Mycobacterium tuberculosis* test: It is one of the newly used tests and its sensitivity in lung and TSF has been reported as 79% (39% of culture, 66% of Xpert test) and specificity as 98%.[21,22]

Tests used in the diagnosis of latent tuberculosis: Although interterferon gamma release tests (IGRA) used in the diagnosis of latent tuberculosis infection have been widely used in the diagnosis of tuberculosis infection in recent years, these tests are insufficient to determine the progression from infection to tuberculosis disease.[23] In recent years, the QIAreach QFT test has been used as a new and simple version of Quantiferon-TB Plus (QFT-Plus) in the diagnosis of latent tuberculosis infection. This test is portable, easy to use, does not require experienced personnel, and uses a single tube for testing. With fluorescence lateral flow reader, it can give quantitative results in 20 minutes and a single tube is sufficient for the test. With this feature, the test can be used at the bedside and does not require laboratory infrastructure.[24]

CONCLUSION

Today, lung extra-pulmonary forms of tuberculosis are still an important public health problem. Thanks to the effective control measures implemented in Turkey, there has been a significant decrease in the number of tuberculosis patients, which was an important public health problem more than a decade ago. In spite of this, lung TB and ADT can be seen as opportunistic infection factors, especially in HIV/AIDS positive patients. In addition, ADT forms should be kept in mind in the clinical differential diagnosis with different organ and system involvement and nonspecific findings. In order to maintain this decrease in the number of tuberculosis cases, it is also of great importance to maintain community health and preventive treatment services for tuberculosis before the COVID-19 pandemic.

ETHICAL DECLARATIONS

Referee Evaluation Process: Externally peer-reviewed.

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REFERENCES

1. Cesur S. Dünyada ve Türkiye'de tüberküloz epidemiyolojisi. *Mikrobiyol Bult.* 2004;38: 461-468.
2. Global Tuberculosis Report 2021. Available online: https://www.who.int/news-room/factsheets/detail/ tuberculosis
3. "Türkiye'de Verem Savaşı 2019 Raporu", Sağlık Bakanlığı Yayın No: 1168, Ankara, 20220.
4. Fitzgerald DW, Sterling TR, Haas DW. *Mycobacterium tuberculosis.* Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases 9th 2020. p. 2985-3021.
5. "Tüberküloz Tanı ve Tedavi Rehberi", Sağlık Bakanlığı Yayın No 1129, Ankara, 2019. https://hsgm.saglik.gov.tr/depo/birimler/tuberkuloz_db/haberler/Tuberkuloz_Tani_Ve_Tedavi_Rehberi_/Tuberkuloz_Tani_ve_Tedavi_Rehberi.pdf
6. Kohli M, Schiller I, Dendukuri N, et al. Xpert MTB/RIF Ultra and Xpert MTB/RIF assays for extrapulmonary tuberculosis and rifampicin resistance in adults. *Cochrane Database Syst Rev.* 2021;1(1):CD012768. doi: 10.1002/14651858.CD012768.pub3
7. Mert A. Miliyer tüberküloz: endemik bölgede pratik tanı yaklaşımı. *Flora.* 2011;16(4):141-145.
8. Taşova Y, Saltoğlu N,Yaman A, Aslan A, Dündar İH. Erişkin tüberküloz menenjit :17 olgunun değerlendirilmesi. *Flora Dergisi.* 1997;1:55-60.
9. Doğanay M. Tüberküloz menenjit. İçinde: İnfeksiyon Hastalıkları, (eds) Topçu AW, Söyletir G, Doğanay M. İstanbul, Nobel Tıp Kitabevleri, 2002;1014-1018.
10. Sümbül M. Tüberküloz menenjit. 21. Yüzyılda Tüberküloz Sempozyumu ve II. Tüberküloz Laboratuvar Tanı Yöntemleri Kursu, Samsun, 2002, Sempozyum Kitabı, s.115-118. https://www.klimik.org.tr/wp-content/uploads/2012/02/982011124450-Mustafa_Sunbul.pdf
11. Ai L, Feng P, Chen D, Chen S, Xu H. Clinical value of interferon-γ release assay in the diagnosis of active tuberculosis. *Exp Ther Med.* 2019;18(2):1253-1257. doi: 10.3892/etm.2019.7696

12. Quinn CM, Kagimu E, Okirworth M, et al. Fujifilm SILVAMP TB LAM assay on cerebrospinal fluid for the detection of tuberculous meningitis in adults with human ımmunodeficiency virus. *Clin Infect Dis*. 2021;73(9):e3428-e3434. doi: 10.1093/cid/ciaa1910
13. Kumar R, Das RK, Mahapatra AK. Role of interferon gamma release assay in the diagnosis of Pott disease. *J Neurosurg Spine*. 2010;12(5):462-6. doi: 10.3171/2009.10.SPINE093
14. Eraksoy H. Gastrointestinal and abdominal tuberculosis. *Gastroenterol Clin North Am*. 2021;50(2):341-360. doi: 10.1016/j.gtc.2021.02.004.
15. Tanoglu A, Erdem H, Friedland JS, et al. Clinicopathological profile of gastrointestinal tuberculosis: a multinational ID-IRI study. *Eur J Clin Microbiol Infect Dis*. 2020;39(3):493-500. doi: 10.1007/s10096-019-03749-y
16. Vaid U, Kane GC. Tuberculous peritonitis. *Microbiol Spectr*. 2017; 5(1). doi: 10.1128/microbiolspec. TNMI7-0006-2016.
17. Aydın F. Deri tüberkülozu. 21. yüzyılda tüberküloz sempozyumu ve II. Tüberküloz laboratuvar tanı yöntemleri kitabı, KLİMİK Derneği, Sempozyum Kitabı, Samsun: 123-129. https://www.klimik.org.tr/kutuphane/klimik-kitaplari/21-yuzyilda-tuberkuloz-sempozyumu-ii-tuberkuloz-laboratuvar-tani-yontemleri-kursu/
18. Taşpınar A, Erdem C. Deri tüberkülozları. *Türkiye Klinikleri Dergisi*. 1985;5(4):325-332.
19. Hatipoğlu ÇA, Cesur S, Bulut C, et al. Addison hastalığı ile renal tüberküloz birlikteliği. *Turk J Clin Lab*. 2019; 10: 262-264.
20. Donovana J, Guy E, Thwaitesa JH. Tuberculous meningitis: where to from here? *Curr Opin Infect Dis*. 2020;33(3):259-266.
21. Jing-Wen Ai, Xian Zhou, Teng Xu, et al. CRISPR-based rapid and ultra-sensitive diagnostic test for *Mycobacterium tuberculosis*. *Emerging Microbes Infections*. 2019, doi.org/10.1080/22221751. 2019.1664939
22. Erdem H, Akova M. Leading infectious diseases problems in Turkey. *Clin Microbiol Infect*. 2012;18(11):1056-1067. doi: 10.1111/1469-0691.12000
23. Goletti D, Delogu G, Matteelli A, Migliori GB. The role of IGRA in the diagnosis of tuberculosis infection, differentiating from active tuberculosis, and decision making for initiating treatment or preventive therapy of tuberculosis infection. *Int J Infect Dis*. 2022; 124 Suppl 1: S12-S19. doi: 10.1016/j.ijid.2022.02.047
24. Miotto P, Goletti D, Petrone L. Making IGRA testing easier: First performance report of QIAreach QFT for tuberculosis infection diagnosis. *Pulmonology*. 2022;28(1):4-5.doi:10.1016/j.pulmoe